Exhibit 10

HIGHLY CONFIDENTIAL: SUBJECT TO PROTECTIVE ORDER

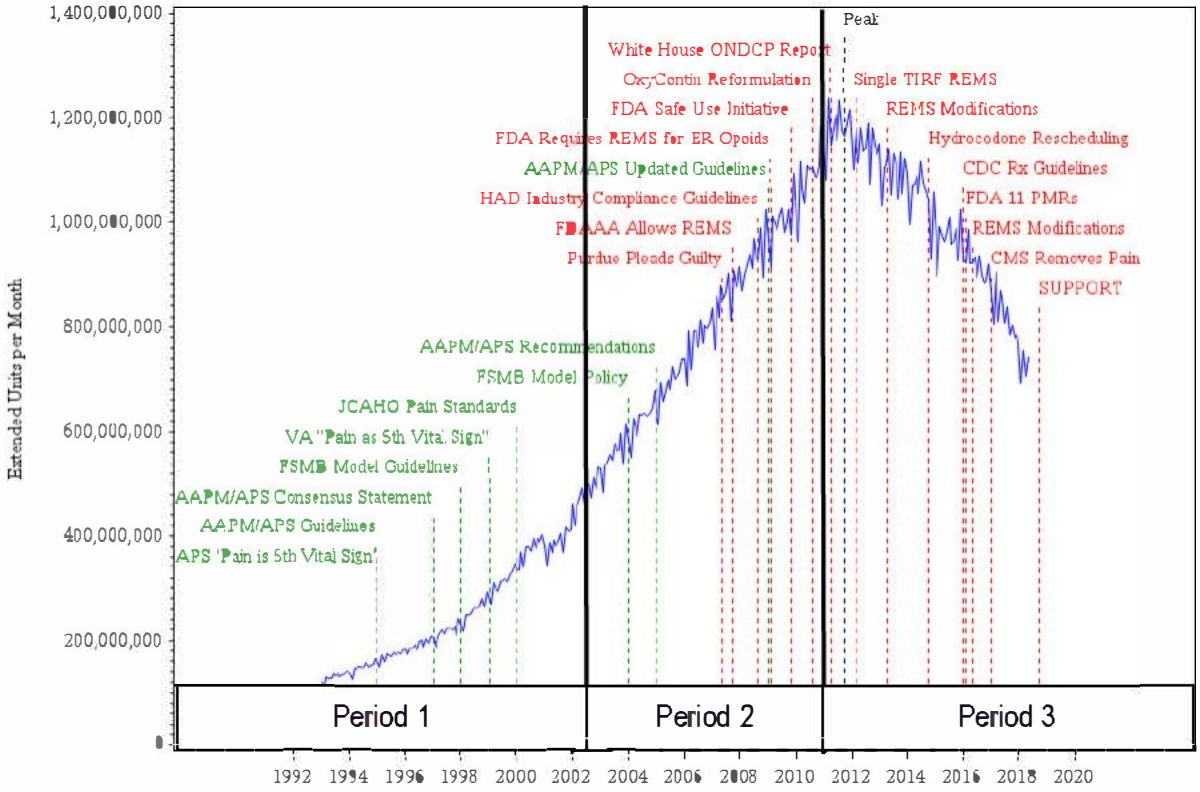
IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF OHIO EASTERN DIVISION

IN RE NATIONAL PRESCRIPTION OPIATE LITIGATION *County of Summit, Ohio, et al.* v. *Purdue Pharma L.P., et al.* *The County of Cuyahoga* v. *Purdue Pharma L.P., et al.*	CASE NO. 1:17-MD-2804 JUDGE POLSTER TRACK ONE CASES

EXPERT REPORT OF PROFESSOR MARGARET K. KYLE

May 10, 2019

Figure 35: Professor Rosenthal's "Timeline of Key Events" and the three periods of her model



Source: IQVIA NPA, ARCOS, CDC.

(134) In fact, Professor Rosenthal develops no *a priori* hypotheses for why/when these turning points exist. Instead, she estimates her model 1,176 times, each with a different combination of turning points, and selects the specification that has the highest Wald statistic. This atheoretical approach to modelling is generally discouraged in economics, and it invalidates the statistical assumptions required for inference. A prominent economist and statistician at UCLA, Edward Leamer, describes the issue as follows:

> The econometric art as it is practiced at the computer terminal involves fitting many, if not thousands, of statistical models. One or several that the researcher finds pleasing are selected for reporting purposes…all the concepts of traditional theory…utterly lose their meaning by the time an applied researcher pulls from the bramble of computer output the one thorn of a model he likes best, the one he chooses to portray as a rose.[258]

[258] Edward E. Leamer, "Let's Take the Con out of Econometrics," The American Economic Review 73, no. 1 (1983), 36–37.

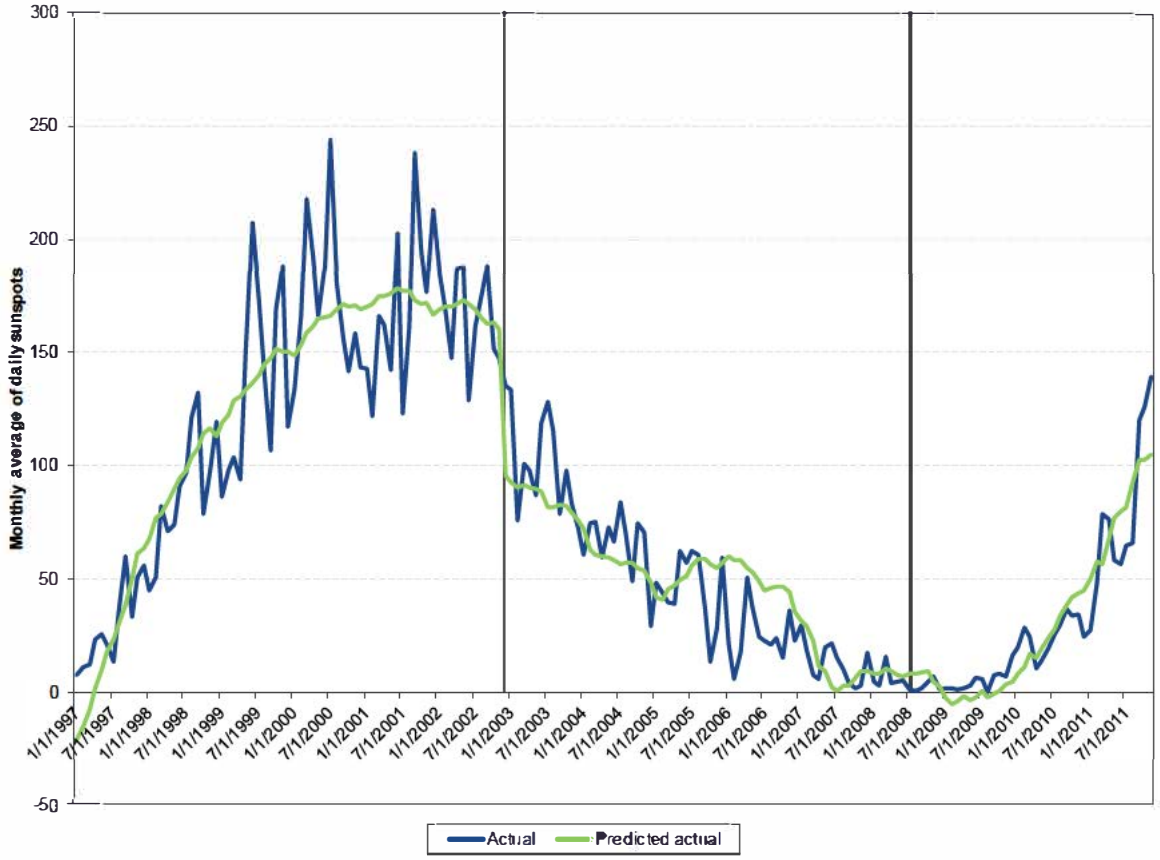
(135) To illustrate the flaws in this approach, I run an alternate version of Professor Rosenthal's model in which I replicate her methodology, but rather than predicting the number of MMEs sold, I use her approach to predict an unrelated variable. For this analysis, I use data from NASA on the monthly average of daily sunspots from January 1997 through November 2011. Similar to Professor Rosenthal, I allow the model to select two turning points based on the maximum Wald statistic and allow the model to estimate the depreciation rate. For Model C, I use the same events as Professor Rosenthal, with the exception of the Hydrocodone Rescheduling date because this falls outside of the range of sunspot data. Figure 36 below summarizes the coefficients on the variables for Model B and Model C, and Figure 37 below illustrates the actual and predicted values for Model B. Despite the fact that manufacturer detailing and opioid prices definitively do not cause sunspots, the coefficients on the three detailing stock variables and the price index are statistically significant. Furthermore, the model fits the sunspot data well, with an adjusted R-squared of 0.88, suggesting that detailing and price explain 88% of the variation in sunspots.

Figure 36: Impact of detailing on monthly average of daily sunspots

Parameter	Label	Model B		Model C	
		Estimate	Sig.	Estimate	Sig.
a	Constant	154	***	87	**
b1	Stock of Promotion (All promotion)*Regime Dummy until Dec2002	0.0003	***	0.0004	***
b2	Stock of Promotion (All promotion)*Dummy from Dec2002	0.0002	***	0.0003	***
b3	Stock of Promotion (All promotion)*Dummy Trend from Jul2008	0.000002	***	0.000002	***
evt1	Consensus Statement From AAPM/APS 01/1998			-30	**
evt2	Federation of State Medical Boards Guidelines 01/1999			-6	
evt3	JCAHO pain standards releases 01/2001			-26	**
evt4	OxyContin Reformulation 08/2010			-21	
main0	Fisher Ideal Price Index	-172	***	-107	***
x	Depreciation constant	0.0648	***	0.0545	***
RSquare		0.8787		0.8883	
AdjRSq		0.8752		0.8823	

Source: Rosenthal backup data; NASA sunspot data. *** indicates 1%; ** indicates 5% significance; * indicates 10% significance.

Figure 37: Actual vs. predicted monthly average of daily sunspots



Source: Rosenthal backup data; NASA sunspot data. *** indicates 1%; ** indicates 5% significance; * indicates 10% significance.

(136) Professor Rosenthal's model is thus a goal-seeking exercise to maximize the relationship between promotion and MMEs. Allowing the data to determine the depreciation rate and turning points with arbitrary interactions makes the model flexible enough to fit almost any pattern, from opioid prescription MMEs to a completely unrelated time series. This approach yields results that are contrary to economic theory and to common sense, and renders her model incapable of demonstrating or quantifying a causal relationship between promotion and MMEs.

VI.C. Professor Rosenthal's direct and indirect causation models ignore myriad other factors that influence prescribing, including many identified by other Plaintiff experts

(137) Professor Rosenthal's models purport to measure the percentage of MMEs "caused by unlawful promotion" using an "econometrically sound method."[259] But in her preferred direct model, Professor

[259] Rosenthal Rep. ¶ 11, 74.

Rosenthal tests only detailing and price, assuming that no other factors—including those she herself identifies—have any effect on prescribing. This issue is not limited to Professor Rosenthal's preferred model, however.[260] In this section, I identify several potentially confounding factors that Professor Rosenthal fails to include in any of her models. In failing to consider certain factors that might explain the variation in opioid MMEs, Professor Rosenthal ignores basic principles of econometrics and generates a model that is incapable of establishing causality.[261]

(138) As Professor. Daniel L. Rubinfeld explains (in the text cited by Professor Cutler to introduce his direct model):

> **An attempt should be made to identify additional known or hypothesized explanatory variables, some of which are measurable and may support alternative substantive hypotheses** that can be accounted for by the regression analysis.
>
> …
>
> **Failure to include a major explanatory variable** that is correlated with the variable of interest in a regression model **may cause an included variable to be credited with an effect that actually is caused by the excluded variable**. In general, omitted variables that are correlated with the dependent variable reduce the probative value of the regression analysis. The importance of omitting a relevant variable depends on the strength of the relationship between the omitted variable and the dependent variable and the strength of the correlation between the omitted variable and the explanatory variables of interest. Other things being equal, the greater the correlation between the omitted variable and the variable of interest, the greater the bias caused

[260] Professor Rosenthal's indirect model includes a handful of demographic variables, but ignores the other factors I describe that have known relationships to prescribing. Though I focus my discussion on these factors omission from her direct (preferred) model, these same factors would also cause her to overstate the effect of the alleged misconduct in her indirect model.

[261] Professor Rosenthal's prioritization of fit and predictive power over the inclusion of relevant explanatory variables is more appropriate for a predictive model than for a causal model.

"Three essential features of model choice are (1) choice of functional form, (2) choice of explanatory variables (regressors) to be included in the model, and (3) whether the multiple regression model assumptions MR1-MR6, listed in Chapter 5, hold….For choice of functional form and regressors, economic principles and logical reasoning play a prominent and vital role. We need to ask: What variables are likely to influence the dependent variable y?...Omission of a relevant variable (defined as one whose coefficient is nonzero) leads to an estimator that is biased. Naturally enough, this bias is known as omitted-variable bias…The possibilities of omitted variable bias or inflated variances from irrelevant variables mean that it is important to specify an appropriate set of explanatory variables." *See, e.g.,* R. Carter Hill and William E. Griffiths, *Principles of Econometrics*, Fourth ed. (Danvers, MA: John Wiley & Sons, 2011), 234–236.;

"Regression coefficients cannot be interpreted as causal if the relationship can be attributed to an alternate mechanism." Kenneth Frank, "Impact of a Confounding Variable on a Regression Coefficient," Sociological Methods & Research 29, no. 2 (2000), 147.

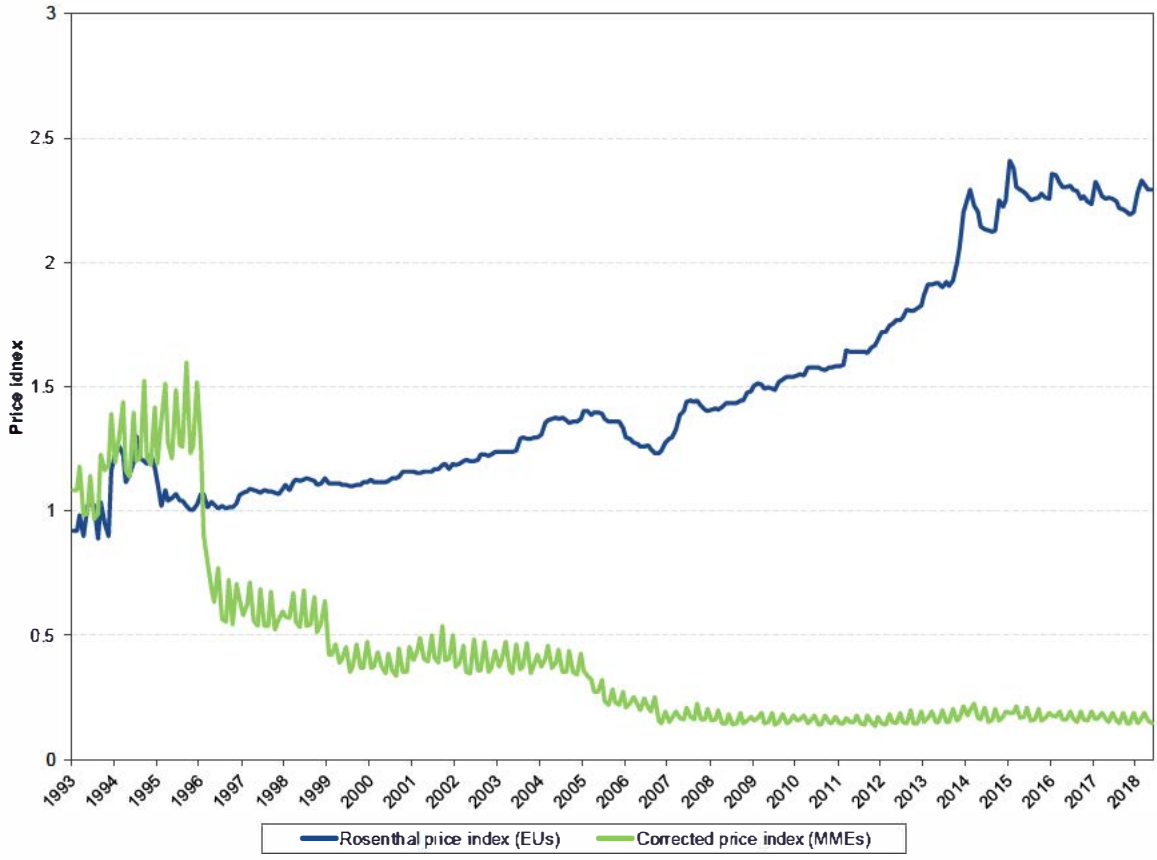
(146) The one variable Professor Rosenthal does attempt to account for in her direct model is price, and she notes "[t]he price index…is statistically significant and in the expected direction (higher prices lead to lower MMEs)."[280]

As Professor Rosenthal's price index increases through time, as seen in the blue line in Figure 39, her models predicts a corresponding decrease in MMEs—the net effect of which is to attribute an even greater share of the actual increase in MMEs to manufacturer promotion. But this prediction is the result of an error in Professor Rosenthal's calculation of the price index.[281] Correcting this error demonstrates that the price index is actually falling through the period in which MMEs are increasing. Theoretically, falling prices would at least in part explain expanding MMEs.

[280] Rosenthal Rep. ¶ 70.

[281] Professor Rosenthal measures the average price per extended unit, and finds an increasing price as more extended release products are introduced, which involve higher MMEs and longer duration associated with few units. But because Professor Rosenthal is attempting to explain changes in MMEs, the correct price index would use the price per MME.

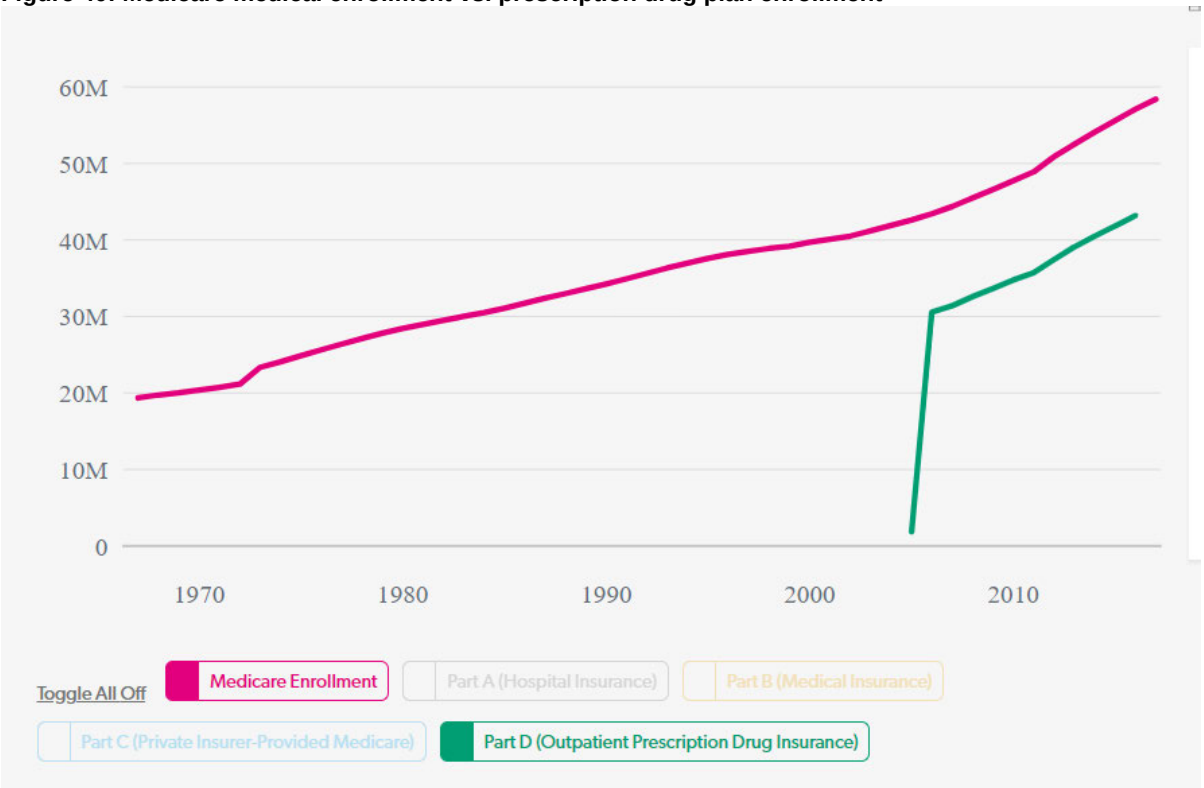
Figure 39: Rosenthal actual and corrected price indices



Source: Rosenthal backup data.

(147) Both of Professor Rosenthal's models also fail to account for changes in prescription drug coverage, which would be expected to increase prescribing. Professor Rosenthal's indirect model does include a broad measure of percent insured, but this is insufficient for two reasons. First, it fails to consider changes in formulary status and utilization management controls (step therapy, prior authorization, quantity limits, etc.) that influence the types and volumes of products each insurance plan will reimburse. I understand Mr. Lieberman has discussed these types of factors in more detail in his report. Second, Professor Rosenthal's measure of insurance coverage examines *medical* insurance, not *prescription drug coverage*. The importance of this distinction is illustrated in Figure 40 below. Enrollment in the Medicare medical benefit, represented by the pink line, has grown at a steady pace since 1970. Medicare retail pharmacy benefits were not provided until 2006, at which point approximately 30 million beneficiaries enrolled (as shown in the green line). Professor Rosenthal's measure of insurance is based on the equivalent of the pink line and fails to account for the large increase in drug coverage that occurs during the same period opioid prescribing is increasing.

Figure 40: Medicare medical enrollment vs. prescription drug plan enrollment



Source: "Medicare Enrollment: Type of enrollment," USA Facts, available at https://usafacts.org/metrics/55637?breakdown=55540&metrics=%7B%2255540%22%3A%5Btrue%2Cfalse%2Cfalse%2Cfalse%2Ctrue%5D%7D

(148) The effects of omitted variables are particularly pronounced in Professor Rosenthal's indirect model, in which she attributes to manufacturers ~50% more opioid MMEs than in her direct model.

VI.D. Professor Rosenthal's "under-treated pain" analysis ignores FDA-approved and other uses of opioids that are potentially appropriate

(149) Professor Rosenthal's "under-treated pain" analysis considers, in reference to Plaintiffs' clinical experts, only a narrow set of appropriate uses of opioids. This set excludes other uses of opioids that I understand are FDA approved and that I understand may be otherwise clinically appropriate under prevailing medical standards. Professor Rosenthal purports to calculate a "[m]aximum [p]ercent of MMEs [e]xplained by [c]linically [j]ustifiable [u]ses," defined as end-of life cancer patients, trauma patients, and surgery patients.[282] She does this by defining inputs that measure volume, a daily dose of MMEs, and a duration of treatment, for each of those three categories (e.g., an end-of-life cancer patient is permitted 64 days of treatment at 80 MMEs per day). She also conducts a "sensitivity" that

[282] Rosenthal Rep. ¶ 100, Table 6.

increases her calculated MMEs for "under-treated pain" by 50%, which she claims allows for "any input [to] increase[] by 50% (or smaller increases in several inputs that yielded an overall increase of 50%...)."[283]

(150) Though Professor Rosenthal describes her analysis as an "upper bound" and notes that she allows "any input [to] increase[] by 50%," her approach is particularly sensitive to changes to how her inputs are defined.[284] For example:

- If it were determined that *all* cancer patients were eligible for opioid treatment instead of only those in the final two months of life, her sensitivity would have to allow more than a 100% increase in the number of cancer patients, as shown in Figure 41 (and would presumably also have to allow the *duration* of treatment to increase beyond the two months she allows). As Figure 41 compares only *new cases* to mortality, the real increase may be much larger than 100%.

Figure 41: CDC cancer deaths and new cases by year

Source: "Cancer Stat Facts: Cancer of Any Site," National Cancer Institute, https://seer.cancer.gov/statfacts/html/all.html

- If it were determined that a more expansive category of trauma visits were necessary, Professor Rosenthal's model might similarly require a sensitivity larger than 50%. To illustrate, I identify emergency department visits involving diagnoses relating to "trauma," "fracture," "sprain," "injury," or "open wound." If these emergency visits required opioid therapy, trauma visits would increase by 72-82%.

283 Rosenthal Rep. ¶ 101.

284 Rosenthal Rep. ¶¶ 92–93 fn 121.

Figure 42: Trauma visits not captured by Professor Rosenthal's analysis

Year	Trauma visits (Rosenthal)	Trauma visits (adjusted)	Percent increase
2014	21,340,310	38,386,731	80%
2013	21,082,463	38,035,529	80%
2012	21,682,661	39,402,930	82%
2011	21,581,931	38,751,128	80%
2010	21,896,672	38,828,309	77%
2009	21,439,290	37,692,832	76%
2008	21,682,517	38,053,364	76%
2007	21,473,036	37,901,281	77%
2006	21,559,556	36,769,881	71%

Source: HCUP Emergency Department National Statistics. Diagnoses--Clinical Classification Software (CCS), All-Listed Diagnosis: #207 Pathological fracture, #225 Joint disorders and dislocations, trauma-related, #226 Fracture of neck of femur (hip), #227 Spinal cord injury, #228 Skull and face fractures, #229 Fracture of upper limb, #230 Fracture of lower limb, #231 Other fractures, #232 Sprains and strains, #233 Intracranial injury, #234 Crushing injury or internal injury, #235 Open wounds of head, neck, and trunk, #236 Open wounds of extremities, #239 Superficial injury, contusion, #244 Other injuries and conditions due to external causes, #662 Suicide and intentional self-inflicted injury, All ED Visits.

- If it were determined that opioid therapy were appropriate for trauma visits to urgent care centers or facilities other than emergency departments, Professor Rosenthal's estimates could also understate the maximum "appropriate" amount of MMEs. A recent study of commercial claim lines found that "urgent care centers showed an increase in claim lines of 1,725 percent—a growth rate more than seven times that of ER claim lines (229 percent)" during the period 2007-2016.[285]

(151) Professor Rosenthal also excludes from her analysis treatment for several conditions that on the face of Kadian's label appear to have been approved by the FDA. For example, the Kadian label says: "Kadian is an opioid agonist indicated for the management of pain severe enough to require daily, around-the-clock, **long-term** opioid treatment."[286] Professor Rosenthal's analysis does not allow for a single Kadian prescription for "long-term opioid treatment." Including these FDA approved label uses in Professor Rosenthal's model would increase the percentage of MMEs "explained by clinically justifiable uses."

(152) I understand that Dr. Warfield has opined that opioid pain medications can be appropriately prescribed in a wider range of circumstances than those included in Professor Rosenthal's analysis. Further, even for the limited categories of patients Professor Rosenthal does include, I understand Dr. Warfield's opinions suggest Professor Rosenthal's interpretation of them is too narrow. For example, I understand Dr. Warfield opines that opioids may appropriately be used to treat non-end of life

285 FAIR Health, "FH Healthcare Indicators and FH Medical Price Index: A New View of Place of Service Trends and Medical Pricing," 2018, p.2, available at https://s3.amazonaws.com/media2.fairhealth.org/whitepaper/asset/FH%20Medical%20Price%20Index%20and%20FH%20Healthcare%20Indicators--whitepaper.pdf.

286 U.S. Food and Drug Administration, "Kadian drug label." Allergan USA, Inc. (2018), available athttps://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020616s061s062lbl.pdf.

cancer patients as well as many more types of trauma patients. Professor Rosenthal acknowledges that certain chronic pain and malignant cancer conditions may require opioid treatment and purports to capture certain "other conditions [that] may be appropriately treated with opioids," but she offers no measure of predicted volume associated with these other conditions or evidence that her 50% sensitivity would sufficiently account for them.[287]

(153) Though I have not undertaken an assessment of each of Professor Rosenthal's inputs, if any—diagnoses categories, volume, appropriate dosage, or appropriate days of supply—are found to be incorrect, her model would likely significantly understate the appropriate level of pain treatment and would therefore not allow her to assess whether "under-treated pain" has contributed to increased MMEs.[288]

VI.E. Professor Cutler's and Professor Gruber's analyses relating opioid shipments to harm ignore myriad other factors

(154) Similar to Professor Rosenthal, Professor Cutler and Professor Gruber also claim a causal relationship between shipments and opioid-related harm.[289] But like Professor Rosenthal, both ignore a number of confounding factors that likely relate to opioid shipments, opioid harm, or both. Indeed, Professor Cutler acknowledges as much with respect to his indirect model—but the statement is just as true for his direct model.[290]

> The indirect regression attributes the entirety of unexplained opioid-related mortality to shipments. To the extent that other factors not modelled in the "baseline" regression contributed to increases in opioid mortality, the indirect approach has the potential to overstate the impact of defendants' actions.[291]

(155) One factor Plaintiffs' experts fail to control for is the focus of the paper on which Professor Cutler based his model. In that paper, Professor Anne Case and Professor (and Nobel laureate) Angus Deaton analyze "deaths of despair" and the recent increase in drug overdoses, suicides, and alcohol.[292] They argue that present economic conditions do not explain increased mortality, and

---

287 Rosenthal Rep. ¶¶ 92–93 fn 121.

288 Professor Rosenthal also had access to insurance claims data with which to analyze individual prescriptions to determine, for example, the frequency of prescriptions in Cuyahoga and Summit county associated with trauma, surgery, and end-of-life cancer, but does not appear to have examined these data. Professor Rosenthal does claim her analysis "can be applied at the county level" but her analysis merely "multiplie[s] by county populations/100,000 persons…to estimate county-level trauma incidents" which does not actually account for county-level variation in clinical needs. Rosenthal Rep. ¶ 102, Appendix D8.

289 Cutler Rep. ¶ 26; Gruber Rep. ¶ 16.

290 The *effect* of omitting such factors would manifest in different ways for the direct and indirect model.

291 Cutler Rep. fn. 53

292 Anne Case and Angus Deaton, "Mortality and morbidity in the 21st century," *Brookings Papers on Economic Activity*,

instead attribute such deaths to "cumulative disadvantage" from a variety of long-term factors that would not be captured by Professors Cutler and Gruber's short-term economic variables in their models. Professor Cutler commented on the paper in agreement:[293]

> In their earlier paper, Case and Deaton suggested that the ready availability of opioid drugs might have exacerbated the increased mortality, especially that resulting from accidental overdoses. In their current paper, their emphasis has changed a bit. **Rather than emphasizing the supply of pills, they now focus on the social and economic circumstances that lead people to take them.**
>
> Their overall suggestion is very much in the tradition of Émile Durkheim (1897): People despair when their material and social circumstances are below what they had expected. This despair leads people to act in ways that significantly harm their health. This may have a direct impact on death through suicide, or an indirect impact through heavy drinking, smoking, drug abuse, or not taking preventive medications for conditions such as heart disease. At root is economic and social breakdown.
>
> **This explanation is certainly correct. There is no way to understand the mortality pattern without considering the sources of despair, and the sources of despair must be very deep-seated indeed.** Case and Deaton discuss where this despair may be coming from, and I suspect there is merit in their discussion here as well. That said, **it is extremely difficult for researchers to get at all the aspects that lead individuals to be living a life that they value less than one would hope they would.** Case and Deaton suggest that despair starts early in life, at the time of entering the labor force or before, as expectations about what a "middle-class life" should involve. They **distinguish this from a theory that focuses only on current income, which they say cannot explain all the data** because the median incomes of blacks and Hispanics have been trending in parallel to those of white non-Hispanics; yet these groups have not seen the worsening mortality rates experienced by white non-Hispanics. **Again, I am tempted to believe this**, though the evidence for any particular view about how expectations are formed and what income shocks imply is not as clear as one would like it to be. (Emphasis added.)

(156) In his deposition, Professor Cutler again admitted that "the theory that economic and social breakdown leads people to despair and that they then act in ways that may be harmful, for example,

(2017), 398.

[293] Though Professor Cutler concludes his comment by suggesting a reduction in the supply of opioids, he acknowledges that as a prospective policy solution to address the supply side because "the market has not been able to provide a stable income and social circumstance that people value highly enough to make them want to strive for a long life." Anne Case and Angus Deaton, "Mortality and morbidity in the 21st century," *Brookings Papers on Economic Activity*, (2017), 444–446.